



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ :</p> <p>C07C 217/48, 233/22, 229/14 C07C 237/20, 233/31 C07D 311/90, 335/20, 219/02</p>	<p>A1</p>	<p>(11) International Publication Number: WO 93/01159</p> <p>(43) International Publication Date: 21 January 1993 (21.01.93)</p>						
<p>(21) International Application Number: PCT/GB92/01212</p> <p>(22) International Filing Date: 3 July 1992 (03.07.92)</p> <p>(30) Priority data:</p> <table border="0"> <tr> <td>9114886.6</td> <td>10 July 1991 (10.07.91)</td> <td>GB</td> </tr> <tr> <td>9208141.3</td> <td>14 April 1992 (14.04.92)</td> <td>GB</td> </tr> </table> <p>(71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): SAARI, Walfred, Spencer [US/US]; 1740 Wagon Wheel Lane, Lansdale, PA 19446 (US). VAN NIEL, Monique, Bodil [NL/GB]; 32 The Shaws, Welwyn Garden City, Hertfordshire AL7 7HR (GB). WILLIAMS, Brian, John [GB/GB]; 73 Godfrey Way, Great Drunmow, Essex CM6 2SE (GB).</p>		9114886.6	10 July 1991 (10.07.91)	GB	9208141.3	14 April 1992 (14.04.92)	GB	<p>(74) Agent: BARRETT-MAJOR, Julie, Diane; Merck & Co., Inc., European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p> <p>(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
9114886.6	10 July 1991 (10.07.91)	GB						
9208141.3	14 April 1992 (14.04.92)	GB						
<p>(54) Title: FUSED TRICYCLIC COMPOUNDS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN THERAPY</p> <div style="text-align: center; margin: 20px 0;"> <p>(I)</p> </div> <div style="text-align: center; margin: 20px 0;"> <p>(a)</p> </div> <p>(57) Abstract</p> <p>Compounds of formula (I), and salts and prodrugs thereof, wherein Q represents a group (a) where W represents a bond, O, S, -CH₂CH₂-, -CH=CH- or NR⁶; and one or both of the phenyl rings may be replaced by a heteroaryl moiety; X and Y each represent H or X and Y together are =O; Z represents O, S or NR⁸; R¹ and R² independently represent H; optionally substituted C₁₋₆ alkyl, optionally substituted phenyl(C₀₋₄alkyl), C₂₋₆ alkylene; COC₁₋₆alkylhalo; COR^a; COOR^a; CONHR^a; COC₁₋₄alkylNR^aR^b; or CONR^aC₁₋₄alkylCONR^aR^b; R³ represents H or C₁₋₆alkyl; R⁴ represents H, C₁₋₆ alkyl or phenyl; R⁵ represents optionally substituted (CH₂)_qphenyl; are tachykinin antagonists, useful for treating pain.</p>								

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FUSED TRICYCLIC COMPOUNDS, PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM AND THEIR USE IN THERAPY

5 This invention relates to a class of tricyclic compounds, which are useful as tachykinin receptor antagonists.

 The tachykinins are a group of naturally-
occurring peptides found widely distributed throughout
10 mammalian tissues, both within the central nervous system
and in the peripheral nervous and circulatory systems.
The structures of three known mammalian tachykinins are
as follows:

Substance P:

15 Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH₂

Neurokinin A:

His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH₂

Neurokinin B:

Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH₂

20 Substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka et al, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 Substance P in the Nervous System, Ciba Foundation
25 Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" TIPS (Dec. 1987) 8 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg et al, J. Med Chem, (1982) 25 1009) and in arthritis [Levine et
30 al in Science (1984) 226 547-549]. These peptides have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh et al in Neuroscience (1988) 25 (3) 817-37 and D. Regoli in "Trends in Cluster Headache" Ed.

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Sicuteri et al Elsevier Scientific Publishers, Amsterdam (1987) page 85)]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd et al "A Neurogenic Mechanism for Symmetrical Arthritis" in The Lancet, 11 November 1989 and Grönblad et al "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in J. Rheumatol. (1988) 15(12) 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis [O'Byrne et al in Arthritis and Rheumatism (1990) 33 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet et al Can. J. Pharmacol. Physiol. (1988) 66 1361-7], immunoregulation [Lotz et al Science (1988) 241 1218-21 and Kimball et al, J. Immunol. (1988) 141 (10) 3564-9], vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh et al, PNAS (1988) 85 3235-9] and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes [Yankner et al, Science (1990) 250, 279-82], in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome. Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod et. al., poster to be presented at C.I.N.P. XVIIIth Congress, 28th June-2nd July, 1992, in press], and in disorders of bladder function such as bladder detrusor hyper-reflexia (Lancet, 16th May, 1992, 1239).

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and

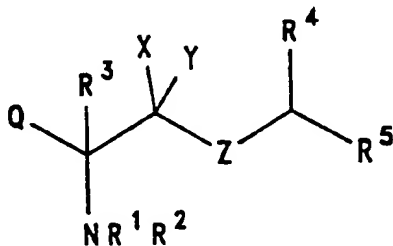
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Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythematosus (European patent application no. 0 436 334), opthalmic disease such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent application no. 0 394 989).

In view of their metabolic instability, peptide derivatives are likely to be of limited utility as therapeutic agents. It is for this reason that non-peptide tachykinin receptor antagonists are sought.

In essence, this invention provides a class of potent non-peptide tachykinin receptor antagonists. By virtue of their non-peptide nature, the compounds of the present invention do not suffer from the shortcomings, in terms of metabolic instability, of known peptide-based tachykinin receptor antagonists.

The present invention provides a compound of formula (I), or a salt or prodrug thereof:

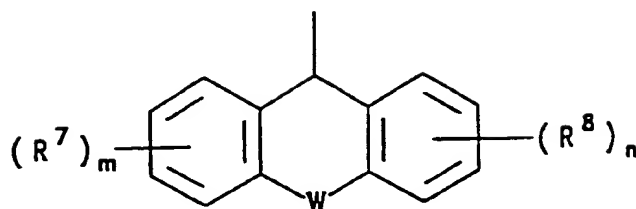


(I)

wherein

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Q represents a group



- 10 where W represents a bond, O, S, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$ or a group NR^6 , where R^6 is H or C_{1-6} alkyl and one or both of the phenyl rings may be replaced by a heteroaryl moiety;
 X and Y each represent H or X and Y together form a group $=\text{O}$;
- 15 Z represents O, S or NR^8 , where R^8 represents H or C_{1-6} alkyl;
- R^1 and R^2 independently represent H; C_{1-6} alkyl optionally substituted by hydroxy, cyano, COR^a , COOR^a , CONR^aR^b , $\text{COC}_{1-4}\text{alkylNR}^a\text{R}^b$, $\text{CONR}^a\text{C}_{1-4}\text{alkylCONR}^a\text{R}^b$ or NR^aR^b , (where R^a and R^b each independently represent H, C_{1-6} alkyl, phenyl (optionally substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl) or phenyl(C_{1-4} alkyl) (optionally substituted in the phenyl ring by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl)); phenyl(C_{1-4} alkyl), (optionally substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo and trifluoromethyl in the phenyl ring); C_{2-6} alkylene; $\text{COC}_{1-6}\text{alkylhalo}$; COR^a ; COOR^a ; CONHR^a ; $\text{COC}_{1-4}\text{alkylNR}^a\text{R}^b$; or $\text{CONR}^a\text{C}_{1-4}\text{alkylCONR}^a\text{R}^b$; (where R^a and R^b are as previously defined) or R^1 and R^2 together form a chain $(\text{CH}_2)_p$ where p is 4 or 5 and where one non-terminal methylene group may optionally be replaced by an oxygen atom or a group NR^x , where R^x is H or C_{1-6} alkyl;
- 30 R^3 represents H or C_{1-6} alkyl;

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R^4 represents H, C_{1-6} alkyl or phenyl (optionally substituted by one or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^C , SOR^C , SO_2R^C , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ or $CONR^C R^d$, where R^C and R^d each independently represent H, C_{1-6} alkyl, phenyl or trifluoromethyl);

R^5 represents $(CH_2)_q$ phenyl, wherein q is 0, 1, 2 or 3 which may optionally be substituted in the phenyl ring by one or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^C , SOR^C , SO_2R^C , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ or $CONR^C R^d$, where R^C and R^d are as above defined;

each R^7 and R^8 independently represents C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^C , SOR^C , SO_2R^C , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ or $CONR^C R^d$, where R^C and R^d are as above defined; and

m and n independently represent 0, 1, 2, 3 or 4.

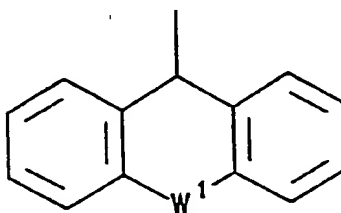
The alkyl, alkenyl and alkynyl groups referred to with respect to any of the above formulae may represent straight, branched or cyclic groups. Thus, for example, suitable alkyl groups include methyl, ethyl, *n*- or *iso*-propyl, *n*-, *sec*-, *iso*- or *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and cycloalkyl-alkyl groups such as cyclopropylmethyl; suitable alkenyl groups include vinyl and allyl; and suitable alkynyl groups include propargyl.

The term "halo" as used herein includes fluoro, chloro, bromo and iodo, especially chloro and fluoro.

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When one or both of the phenyl rings of Q is/are replaced by a heteroaryl moiety, this will suitably be a pyridyl moiety.

A particular subgroup of compounds according to formula (I) is represented by compounds wherein Q represents a group



where W^1 is a bond, O, S or a group NR^6 , where R^6 is H or C_{1-6} alkyl;

15 R^1 and R^2 each independently represent H, C_{1-6} alkyl, phenyl(C_{1-4} alkyl), COR^{10} , $COOR^{10}$ or $CONHR^{10}$, where R^{10} is C_{1-6} alkyl or phenyl;

R^4 represents H, C_{1-6} alkyl or phenyl (optionally substituted by one or more of C_{1-6} alkyl, 20 C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, SCH_3 , $SOCH_3$, SO_2CH_3 , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ or $CONR^C R^d$ (where R^C and R^d are as above defined); and

R^5 represents $(CH_2)_q$ phenyl, wherein q is 0, 1, 25 2 or 3 which may optionally be substituted in the phenyl ring by one or more of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo, cyano, nitro, trifluoromethyl, SCH_3 , $SOCH_3$, SO_2CH_3 , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ or $CONR^C R^d$ (where R^C and R^d are as above defined);

30 wherein any phenyl (including benzyl) ring in the definitions of R^1 or R^2 (including R^{10}) above may be optionally substituted by one or more of C_{1-6} alkyl, C_{1-6} alkoxy, halo or trifluoromethyl.

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In the compounds of the invention, W suitably represents a bond, CH_2CH_2 or $\text{HC}=\text{CH}$.

Preferably Q is 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl, 5H-dibenzo[a,d]cyclohepten-5-yl or 9-fluorenyl.

Preferably X and Y each represent H.

Preferably Z represents oxa.

Suitable values for the groups R^1 and R^2 include H, C_{1-6} alkyl, especially methyl; C_{1-6} alkyl substituted by, for example, cyano, hydroxy, NH_2 , $\text{CO}_2\text{C}_{1-6}$ alkyl and CONH_2 .

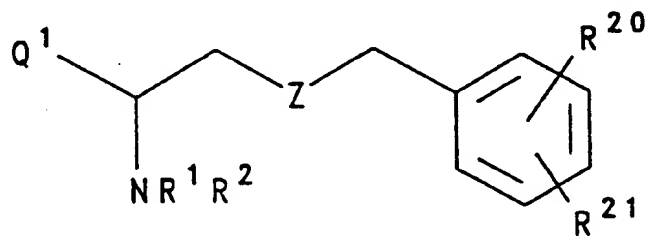
Suitable values for the group R^3 include H and methyl, preferably H.

Preferably R^4 represents H.

Suitably R^5 represents $(\text{CH}_2)_q$ phenyl where q is 0, 1 or 2 and the phenyl is substituted. Suitable phenyl substituents include methyl, methoxy, nitro, cyano, halo and trifluoromethyl. Preferably R^5 represents a substituted phenyl group. More preferably R^5 represents 3,5-dimethylphenyl or 3,5-bistrifluoromethylphenyl.

Preferably m and n each represent O.

A preferred sub-group of compounds according to the invention is represented by formula (Ia)



(Ia)

wherein R^1 , R^2 and Z are as defined for formula (I) above;

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Q^1 represents 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl, 5H-dibenzo[a,d]cyclohepten-5-yl or 9-fluorenyl.

R^{20} and R^{21} each independently represent H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^C , SOR^C , SO_2R^C , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ or $CONR^C R^d$, where R^C and R^d are as above defined; and salts and prodrugs thereof.

Particularly preferred are compounds of formula (Ia) wherein R^{20} and R^{21} are other than hydrogen and are located in the 3- and 5-positions. Most preferably R^{20} and R^{21} each represent methyl or trifluoromethyl.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, oxalic acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Thus, for example, when both R^1 and R^2 are other than hydrogen, the nitrogen atom to which they are attached may be further substituted to give a quaternary ammonium salt. Furthermore, where the compounds of the invention carry

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an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

5 The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible in vivo into the required compound of formula
10 (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

 The compounds according to the invention may
15 exist both as enantiomers and as diastereomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

 The invention also provides pharmaceutical
20 compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or
25 suspensions, or suppositories, for oral, parenteral or rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose,
30 sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-

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toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium

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carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone or gelatin.

The present invention further provides a process for preparing a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of the present invention are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example, diabetic or chemotherapy-induced neuropathy, and postherpetic and other neuralgias; respiratory diseases such as chronic obstructive airways disease, bronchopneumonia, bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis and rheumatoid arthritis; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such

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as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of bladder function such as bladder detrusor hyper-reflexia; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine. For example, the compounds of formula (I) may suitably be used in the treatment of disorders of the central nervous system such as anxiety, psychosis and schizophrenia; neurodegenerative disorders such as senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; respiratory diseases such as bronchospasm and asthma; inflammatory diseases such as inflammatory bowel disease, osteoarthritis and rheumatoid arthritis; adverse immunological reactions such as rejection of transplanted tissues; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera such as ulcerative colitis, Crohn's disease and incontinence; disorders of blood flow caused by vasodilation; and pain or nociception, for example, that attributable to or associated with any of the foregoing conditions or the transmission of pain in migraine.

The compounds of formula (I) are particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as,

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for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and migraine.

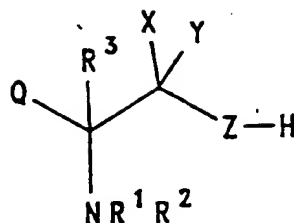
5 The present invention further provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P. The present invention also provides a
10 method for the the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound or composition
15 of this invention.

 In the treatment of conditions involving actions of tachykinins released physiologically in response to noxious or other stimuli, a suitable dosage level is about 0.001 to 50 mg/kg per day, such as 0.001
20 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once daily.

 The compounds according to the invention
25 wherein Z is O or S may be prepared by reaction of a compound of formula (II)

30

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(II)

10 wherein Q, R¹, R², R³, X and Y, are defined as for formula (I) and Z is O or S, with a compound of formula HalCHR⁴R⁵, where R⁴ and R⁵ are as defined for formula (I) and Hal is halo, such as bromo, chloro or iodo, in the presence of a base.

15 The reaction is conveniently carried out in a suitable organic solvent, such as an ether, for example, tetrahydrofuran.

Suitable bases of use in the reaction include alkali or alkaline earth metal hydrides, for example, sodium hydride.

20 The compounds of formula (I) prepared to the above described process may, if necessary or desired be converted to other compounds of formula (I). Thus, for example, the compounds of the invention wherein Z is a group NR⁸ and X and Y together represent =O may be prepared from the compounds of formula (II) wherein Z is O and X and Y together represent =O by reaction with a compound of formula HNR⁸CHR⁴R⁵ in the presence of a coupling agent, such as dicyclohexylcarbodiimide.

30 The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, diethyl ether or tetrahydrofuran.

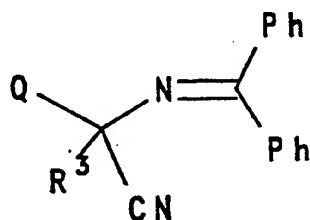
The compounds according to the invention wherein Z is NR⁸ and X and Y are hydrogen may be prepared

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from the corresponding compounds of formula (I) wherein X and Y together represent =O, by reduction.

Suitable reducing agents of use in the reaction include borane and metal hydrides, such as lithium aluminium hydride. The reaction is conveniently effected in a suitable organic solvent, such as an ether, for example, tetrahydrofuran.

Compounds of formula (II) wherein Z is O and X and Y together represent a group =O may be prepared, for example, from intermediates of formula (III)



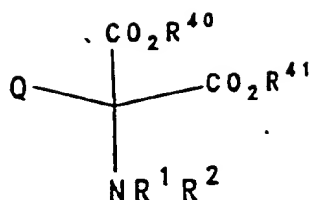
(III)

wherein Q and R³ are as above defined and Ph represents phenyl, by hydrolysis.

The reaction is conveniently effected by heating a solution of the compound of formula (III) in concentrated hydrochloric acid at reflux.

Alternatively, compounds of formula (II) wherein Z is O, X and Y are =O and R³ is H may be prepared from intermediates of formula (IVA)

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(IV)

wherein Q, R¹ and R² are as above defined, and R⁴⁰ and R⁴¹ both represent H (IVA), by decarboxylation.

The reaction is conveniently effected by heating the compound of formula (IVA) in a concentrated mineral acid, such as concentrated hydrochloric acid, to a temperature of about 90-120°C, such as about 100°C.

Compounds of formula (II) wherein Z is O and X and Y are =O may also be prepared by conventional procedures for the preparation of amino acids which are well documented and are described, for example, in Chemistry and Biochemistry of the Amino Acids, ed. G. C. Barrett, Chapman and Hall, 1985.

Compounds of formula (II) wherein Z is S may be prepared from the corresponding compounds of formula (II) wherein Z is O by treating the latter compound with Lawesson's reagent or phosphorus pentasulphide in a suitable solvent, e.g. pyridine, at ambient or elevated temperature, suitably at the reflux temperature of the chosen solvent.

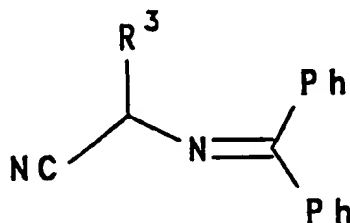
Compounds of formula (II) wherein X and Y represent H may be prepared from the corresponding compounds of formula (II) wherein X and Y together represent =O, by reduction.

Suitable reducing agents include metal hydrides, such as lithium aluminium hydride. The reaction is conveniently effected in a suitable organic

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solvent, such as an ether, for example, tetrahydrofuran, suitably at elevated temperature, such as the reflux temperature of the solvent.

Intermediates of formula (III) may be prepared
5 from compounds of formula (V)



(v)

wherein R³ is as defined for formula (I), by reaction
15 with a compound of formula Q-Hal wherein Hal is halo,
such as bromo, chloro or iodo, in the presence of a base.

Suitable bases of use in the reaction include metal hydroxides, for example, sodium hydroxide. The reaction is conveniently effected in a mixture of water and a suitable organic solvent, such as a hydrocarbon, for example, toluene, in the presence of a phase transfer catalyst, such as benzyltrimethyl ammonium chloride.

Compounds of formula (V) are commercially available or may be prepared by procedures readily apparent to one skilled in the art.

Compounds of formula (IVA) may be prepared from the corresponding compounds of formula (IV) wherein R⁴⁰ and R⁴¹ each represent alkyl (IVB), by saponification.

30 The saponification is conveniently effected using an alkali metal hydroxide, such as sodium hydroxide, in an aqueous solvent, such as aqueous alcohol, for example, aqueous methanol, preferably at elevated temperature, e.g. the reflux temperature of the chosen solvent.

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Compounds of formula (IVB) may be prepared by reaction of a compound of formula Q-Hal as above defined with a malonate derivative of formula $R^{41}O_2CCH(NR^1R^2)CO_2R^{40}$, which malonate derivatives are commercially available or may be prepared from commercially available compounds by conventional means known to those skilled in the art.

Compounds of formula Q-Hal are commercially available or may be prepared by conventional procedures known to those skilled in the art.

Compounds of formula (I) may also be prepared from other compounds of formula (I). Thus, for example, compounds of formula (I) wherein one or both of R^1 and R^2 represent hydrogen may be reacted with an optionally substituted alkylating or an acylating agent to produce compounds of formula (I) wherein one or both of R^1 and R^2 represent an optionally substituted alkyl or an acyl group. Suitable procedures are described in the accompanying examples, or will be readily apparent to one skilled in the art.

Conversely, compounds of formula (I) wherein one or both of R^1 and R^2 represent, for example, an acyl or a benzyl group, may be converted to compounds of formula (I) wherein one or both of R^1 and R^2 represent H by, for example, hydrolysis or catalytic hydrogenation. Suitable reagents and conditions are described in the accompanying examples, or will be readily apparent to one skilled in the art of organic chemistry.

Intermediates of formula (II) are novel compounds. Intermediates of formula (II) and the preparation thereof represent further aspects of the present invention.

Where the above-described process for the preparation of the compounds according to the invention

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gives rise to mixtures of stereoisomers these isomers may, if desired, be separated, suitably by conventional techniques such as preparative chromatography.

5 The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with
10 an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides,
15 followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This
20 may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wutts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The
25 protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

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EXAMPLE 1: 1-(5H-Dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine, oxalate salt

5 a) Through a cooled (-15°C) solution of dibenzosuberanol (20g) and calcium chloride (20g) in toluene (750ml) was bubbled hydrogen chloride gas for 15 minutes. The solution was warmed to room temperature over 1 hour and hydrogen chloride gas bubbled through for a further 20 minutes. After 16 hours the solution was filtered and the filtrate evaporated *in vacuo* to leave 5-chloro-5H-dibenzo[a,d]cycloheptene as a yellow crystalline solid. ¹H NMR (360MHz, CDCl₃) δ 6.25 (1H, bs), 7.14 (2H, s), 7.39-7.45 (8H, m).

10 b) To a stirred suspension of diethyl acetamidomalonate (21.2g) in tetrahydrofuran (150ml) was slowly added sodium hydride (3.4g, 80% dispersion in oil) under an atmosphere of nitrogen. After 1h to this solution was added a solution of 5-chloro-5H-dibenzo[a,d]cycloheptene (20.3g, Example 1a) in tetrahydrofuran (100ml). The solution was heated to reflux for 18h, cooled to room temperature and to this was added a saturated solution of NH₄Cl and ethyl acetate. The organic phase was dried (MgSO₄), concentrated *in vacuo* and the residue chromatographed on silica (eluting with ethyl acetate:petroleum ether bp 60-80°C (1:4)). This gave 2-diethyl(5H-dibenzo[a,d]cyclohepten-5-yl)-2-acetamidomalonate as a yellow solid. ¹H NMR (360MHz, CDCl₃) δ 1.02-1.04 (6H, m), 1.6 (3H, s), 3.82-3.91 (2H, m), 4.0-4.13 (2H, m), 5.78 (1H, s), 6.39 (1H, s), 6.79 (2H, s), 7.21-7.36 (6H, m), 7.54-7.56 (2H, m).

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- c) A mixture of diethyl 2-(5H-dibenzo[a,d]cyclohepten-5-yl)-2-acetamidomalonate (20.2g, Example 1b) and sodium hydroxide (4g) in methanol (75ml) and water (75ml) was heated to reflux for 8h. To the cooled solution was added 1M-HCl until pH = 6. The solution was concentrated *in vacuo* and acidified to pH = 2 by addition of 1M-HCl. The solid which formed was collected by filtration and heated together with 6M-HCl for 3h at 100°C. The cooled solution was filtered and the residue dissolved in hot water, refiltered and to the filtrate was added aqueous ammonia until pH 7-8. The solid which formed on cooling to room temperature was collected by filtration and dried *in vacuo* to give 5H-dibenzo[a,d]cyclohepten-5-ylglycine. ¹H NMR (360MHz, d₄ MeOH), δ 4.08-4.12 (1H, m), 4.35-4.39 (1H, m), 7.0-7.11 (2H, m), 7.24-7.30 (3H, m), 7.34-7.45 (5H, m).
- d) 5-H-Dibenzo[a,d]cyclohepten-5-ylglycine (4.8g, Example 1c) was added in portions to a solution of lithium aluminium hydride (54ml of 1.0M solution) in 30ml dry THF at 0°C. The reaction was allowed to stand at room temperature overnight, quenched with 2N sodium hydroxide and poured through Celite. The filtrate was washed with water, dried over MgSO₄ and solvent removed *in vacuo* to leave a residue which was induced to crystallised in ethyl acetate or dichloromethane to give 5H-dibenzo[a,d]cycloheptene glycinol. ¹H NMR (360MHz, d₄ MeOH) δ 3.05-3.17 (2H, m), 3.29-3.33 (1H, m), 3.89-3.94 (1H, m), 6.90-6.97 (2H, m), 7.23-7.38 (8H, m).

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e) A mixture of 5H-dibenzo[a,d]cycloheptene glycinol (1.13g, Example 1d) and di-*tert*-butyldicarbonate (1.0g) in 10ml CH₂Cl₂ was stirred at room temperature for 1.5h. Solvent was removed *in vacuo* to give N-*tert*-butoxycarbonyl (5H-dibenzo[a,d]cycloheptene) glycinol which could be induced to crystallise in diethyl ether. ¹H NMR (360MHz, CDCl₃) δ 1.24 (9H, s), 2.43 (1H, brs), 3.1-3.3 (1H, m), 3.3-3.5 (1H, m), 4.1-4.2 (1H, m), 4.2-4.4 (1H, m), 4.4-4.6 (1H, m), 6.9-7.1 (2H, m), 7.2-7.4 (8H, m).

f) To a solution of N-*tert*-butoxycarbonyl (5H-dibenzo[a,d]cycloheptene) glycinol (1.49g, Example 1e) and 3,5-dimethylbenzyl bromide (0.92g) in 4ml DMF-THF (1:1) under nitrogen at 0°C was added sodium hydride (130mg, 80% dispersion). The reaction was stirred at room temperature for 2h then partitioned between aqueous NH₄Cl-ethyl acetate. The organic phase was dried (MgSO₄) and solvent removed *in vacuo*. The residue was chromatographed on silica (5% ethyl acetate-petroleum ether eluant) to give N-*tert*-butoxycarbonyl (5H-dibenzo[a,d]cycloheptene) glycinol-3,5-dimethylbenzyl ether. mp 116-118°C (petroleum ether). ¹H NMR (360MHz, CDCl₃) 1.15 (9H, s), 2.36 (6H, s), 2.90-2.93 (1H, m), 3.18-3.21 (1H, m), 4.16-4.37 (4H, m), 4.79-4.82 (1H, m), 6.88-6.94 (4H, m), 7.05-7.08 (1H, m), 7.21-7.32 (8H, m).

g) A solution of N-*tert*-butoxycarbonyl (5H-dibenzo[a,d]cycloheptene) glycinol-3,5-dimethylbenzyl ether (0.55g, Example 1f) in 2ml dry CH₂Cl₂ was treated with

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trifluoroacetic acid (2ml) and stirred for 20 minutes. Solvent and other volatiles were removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with aqueous Na₂CO₃, dried (MgSO₄) and solvent removed *in vacuo*. The residue was dissolved in ethanol and treated with oxalic acid to give the title compound. mp 175-177°C (ethanol-diethyl ether). ¹H NMR (360MHz, DMSO-d₆) 2.27 (6H, s), 2.85-2.87 (1H, m), 3.17-3.19 (1H, m), 3.58-3.40 (1H, m), 4.15-4.40 (3H, m), 6.88 (2H, s), 6.92 (1H, s), 6.99-7.08 (2H, m), 7.28-7.48 (8H, m).

EXAMPLE 2: N-Acetamido-1-(5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine

A solution of the product of Example 1 (0.35g) and acetic anhydride (0.178ml) in 3ml pyridine was allowed to stand overnight. The reaction was partitioned between ethyl acetate and 1N HCl. The organic phase was dried (MgSO₄) and solvent removed *in vacuo*. The residue was chromatographed (20% ethyl acetate-petroleum ether) to give the title compound. mp 115-117°C (ethyl acetate-petroleum ether). ¹H NMR (360MHz, CDCl₃) 1.54 (6H, s), 2.34 (3H, s), 2.92-2.94 (1H, s), 3.19-3.23 (1H, m), 4.20-4.31 (3H, m), 4.65-4.8 (1H, m), 5.5-5.6 (1H, m), 6.90-6.96 (4H, m), 7.01-7.05 (1H, m), 7.21-7.34 (8H, m). Found: C, 81.3; H, 7.3; N, 3.2: Calculated for C₂₈H₂₉NO₂ C, 81.72; H, 7.10; N, 3.40%.

EXAMPLE 3: 1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine, oxalate salt

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5-Chlorodibenzosuberane was treated in an analogous manner to that described in Example 1 to yield the title compound. mp 197-200°C. ¹H NMR (360MHz, DMSO-d₆) δ 2.27 (6H, m), 2.8-3.1 (1H, br m), 3.15-3.25 (1H, m), 3.3-3.5 (3H, m), 4.1-4.2 (2H, m), 4.3-4.35 (1H, m), 4.4-4.5 (1H, m), 6.93 (3H, s), 7.1-7.3 (8H, m). Found: C, 71.83; H, 6.77; N, 2.97; Calculated for C₂₅H₂₉NO.C₂H₂O₄ C, 72.14; H, 6.95; N, 3.12%.

10 EXAMPLE 4: N-Acetamido-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine

The product of Example 3 was acetylated in an analogous manner to that described in Example 2 to give the title compound. mp 109-111°C. ¹H NMR (360MHz, CDCl₃) δ 1.60 (3H, s), 2.35 (6H, s), 2.84-2.91 (2H, m), 3.37 (2H, s), 3.46-3.68 (2H, m), 4.14-4.17 (1H, m), 4.35-4.44 (2H, m), 4.84-4.90 (1H, m), 5.66-5.71 (1H, m), 6.98-7.25 (11H, m). Found: C, 71.83; H, 6.77; N, 2.97; Calculated for C₂₅H₂₉NO.C₂H₂O₄ C, 72.14; H, 6.95; N, 3.12%.

20 EXAMPLE 5: N,N-Dimethyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine, oxalate salt

To a solution of the product of Example 3 (320mg) in 2ml methanol at 0°C was added acetic acid (0.25ml) followed by sodium borohydride (0.1g) and aqueous formaldehyde (0.167ml of 37 wt %). Solvent was removed after 3 days and the residue

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purified by chromatography (1:1 ethyl acetate-petroleum ether eluant). The purified free base was dissolved in diethyl ether and oxalic acid in methanol was added. Solvent was removed to give the title compound. mp 68-69°C (ethyl acetate-petroleum ether). ¹H NMR (360MHz, DMSO-d₆) 2.24 (6H, s), 2.49 (6H, s), 2.8-3.0 (2H, m), 3.32-3.50 (4H, m), 3.8-4.4 (4H, br m), 6.82 (2H, s), 6.88 (1H, s), 7.0-7.3 (8H, m). Found: C, 69.34; H, 6.71; N, 2.64; Calculated for C₂₈H₃₃NO.1.5 (C₂H₂O₄) C, 69.64; H, 6.78; N, 2.62%.

EXAMPLE 6: 1-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-bistrifluoromethylbenzyloxy)ethyl amine, oxalate salt

Prepared in an analogous manner to that described for the product of Example 3. mp 175-176°C. ¹H NMR (360MHz, DMSO-d₆) 2.8-3.0 (2H, m), 3.3-3.6 (3H, m), 4.1-4.3 (2H, m), 4.5-4.7 (2H, m), 7.0-7.4 (8H, m), 8.0-8.1 (3H, m).

EXAMPLE 7: N-Carbomethoxymethyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-bistrifluoromethylbenzyloxy)ethylamine, oxalate salt

A mixture of the title product of Example 6, methyl bromoacetate (one equivalent) and triethylamine (one equivalent) were refluxed in THF for 22h. The reaction was partitioned between diethyl ether-water and the organic phase separated and dried (MgSO₄). Solvent was removed *in vacuo* and the residue redissolved in ethanol. Oxalic acid was added,

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solvent removed *in vacuo*, and the residue recrystallised to give the title compound. mp 160-165°C (ethyl acetate-petroleum ether). ¹H NMR (360MHz, DMSO-d₆) 2.8-3.0 (2H, m), 3.2 (2H, s), 3.4-3.5 (6H, m), 3.6-3.65 (1H, m), 3.9-3.95 (1H, m), 4.5 (3H, s), 7.00-7.2 (8H, m), 7.9 (3H, s).

EXAMPLE 8: N-Carbamoylmethyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-bistrifluoromethylbenzyloxy)ethylamine, oxalate salt

A solution of the product of Example 6 in 5ml methanol saturated with ammonia was sealed in a reaction vessel and left at 0°C for 48h. Solvent was removed *in vacuo*, and the residue dissolved in ethanol. Oxalic acid and water were added to give the title compound. mp 120-122°C. ¹H NMR (360MHz, DMSO-d₆) 2.8-3.0 (2H, m), 3.3-3.7 (6H, m), 4.2-4.6 (4H, m), 7.00-7.4 (8H, m), 7.9 (1H, s), 7.95 (2H, s).

EXAMPLE 9: 3,5-Dimethylbenzyl-2-(9-fluoroenyl)glycinate

a) A solution of N-(diphenylmethylene)glycine ethyl ester (5g) in tetrahydrofuran (15ml) was added dropwise to a cooled solution of lithium diisopropylamide (1 mol eq) in tetrahydrofuran (20ml) and hexane (11ml) at -70°C. After 1h at -70°C, a solution of 9-bromofluorene (4.58g) in tetrahydrofuran (15ml) was added. After stirring the solution for 1h at -70°C and then at room temperature (16h), the solution was diluted with saturated ammonium chloride solution (500ml) and diethyl

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ether (500ml). The organic phase was washed with saturated brine and dried (MgSO_4). After removal of the solvent *in vacuo* the residue was purified on a silica column to give ethyl N-(diphenylmethylene)-(9-fluorenyl)glycinate, 2.2g.

5 b) The product of part (a) (2.2g) was heated at reflux for 16h with 5.5M-hydrochloric acid (30ml). The cooled solution was washed with diethyl ether and the aqueous phase evaporated to dryness. The residue was recrystallised from acetone-water to give 2-(9-fluorenyl)glycine hydrochloride, 0.7g.

10 c) To a solution of the product of part (b) (0.7g) and sodium carbonate (0.95g) in dioxan (5ml) and water (10ml) was added di-t-butylidicarbonate (0.664g). After stirring the solution for 16h at room temperature, water (50ml) and diethyl ether (60ml) were added. To the aqueous phase was added solid citric acid to
15 pH 3 and the product extracted into ethyl acetate (3 x 30ml). The combined organic phases were washed with water, saturated brine, dried (MgSO_4) and evaporated to dryness to give N-t-butoxycarbonyl-2-(9-fluorenyl)glycine 0.75g.

20 d) To a solution of the product of part (c) (0.750g) in methanol (10ml) was added a solution of cesium carbonate (348mg) in water (5ml). The solvent was removed by evaporation and the residue dried by repeated evaporation from dimethylformamide (3 x 30ml). To the residue dissolved in dimethylformamide (50ml) was added 3,5-dimethylbenzyl
25 bromide (0.636g) and the solution stirred at room temperature

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for 16h. The solvent was removed *in vacuo* and the residue partitioned between dichloromethane and water. The organic phase was washed with saturated brine, dried (MgSO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with mixtures of ethyl acetate in petroleum ether bp 60-80°C to give 3,5-dimethylbenzyl-N-t-butoxycarbonyl-2-(9-fluorenyl)glycinate. Trifluoroacetic acid (3ml) was added to the ester (0.2g) and after 40 minutes the solvent was removed by evaporation and a solution of 4-toluenesulfonic acid (84mg) in ethanol (1ml) added to give 3,5-dimethylbenzyl-2-(9-fluorenyl)glycinate, 4-toluenesulphonic acid salt. mp 150-151°C. Found: C, 70.19; H, 5.74; N, 2.61. $\text{C}_{24}\text{H}_{23}\text{NO}_2 \cdot \text{C}_7\text{H}_8\text{SO}_3$ requires C, 70.30; H, 5.90; N, 2.64%. m/z (FAB^+) = 358 ($\text{M}+\text{H}$).

15 EXAMPLE 10: 3,5-Dimethylbenzyl N-acetyl-2-(9-fluorenyl)glycinate

3,5-Dimethylbenzyl N-t-butoxycarbonyl-2-(9-fluorenyl)glycinate (Example 9d, 0.5g) was dissolved in trifluoroacetic acid (10ml) for 40 minutes then evaporated *in vacuo*. To a solution of the residue in pyridine (10ml) was added acetic anhydride (1ml) for 16h. The solvent was removed *in vacuo* and the residue crystallised from diethyl ether/petroleum ether bp 60-80°C to give the title compound mp 162-164°C. Found: C, 78.19; H, 6.26; N, 3.45. $\text{C}_{26}\text{H}_{25}\text{NO}_3$ requires C, 78.17; H, 6.30; N, 3.50%. m/z (CI^+) = 400 ($\text{M}+\text{H}$), (CI^-) = 398 ($\text{M}-\text{H}$).

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The following examples illustrate pharmaceutical compositions according to the invention.

5 EXAMPLE 11A Tablets containing 1-25mg of compound

		<u>Amount mg</u>		
	Compound of formula (I)	1.0	2.0	25.0
	Microcrystalline cellulose	20.0	20.0	20.0
	Modified food corn starch	20.0	20.0	20.0
10	Lactose	58.5	57.5	34.5
	Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 11B Tablets containing 26-100mg of compound

		<u>Amount mg</u>		
15	Compound of formula (I)	26.0	50.0	100.0
	Microcrystalline cellulose	80.0	80.0	80.0
	Modified food corn starch	80.0	80.0	80.0
	Lactose	213.5	189.5	139.5
	Magnesium Stearate	0.5	0.5	0.5
20	The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting			
25	granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.			

EXAMPLE 12 Parenteral injection

	<u>Amount mg</u>
30 Compound of formula (I)	1 to 100mg
Citric Acid Monohydrate	0.75mg
Sodium Phosphate	4.5mg
Sodium Chloride	9mg

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Water for injection to 1ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

EXAMPLE 13 Topical formulation

	<u>Amount mg</u>
Compound of formula (I)	1-10g
10 Emulsifying Wax	30g
Liquid paraffin	20g
White Soft Paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

SUBSTANCE P ANTAGONISM ASSAY

20

A. Receptor Expression in Monkey Kidney Cell Line (COS)

To express the cloned human neurokinin-1- receptor (NK1R) transiently in COS, the cDNA for the human NK1R was cloned into the expression vector pCDM9 which was derived from pCDM8 (INVITROGEN) by inserting the ampicillin resistance gene (nucleotide 1973 to 2964 from BLUESCRIPT SK+ (trademark, STRATAGENE, La Jolla, CA, USA)) into the Sac II site. Transfection of 20 ug of the plasmid DNA into 10 million COS cells was achieved by electroporation in 800 µl of transfection buffer (135 mM NaCl, 1.2 mM CaCl₂, 1.2 mM MgCl₂, 2.4 mM K₂HPO₄, 0.6 mM KH₂PO₄, 10 mM glucose, 10 mM N-2-hydroxyethyl-piperazine-N'-2-ethane sulphonic acid (HEPES) pH 7.4) at 260 V and 950 µF using the IBI GENEZAPPER (trademark IBI, New

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Haven, CT, USA). The cells were incubated in 10% fetal calf serum, 2 mM glutamine, 100U/ml penicillin-streptomycin, and 90% DMEM media (GIBCO, Grand Island, NY, USA) in 5% CO₂ at 37°C for three days before the binding assay.

B. Stable Expression in Chinese Hamster Ovarian Cell Line

To establish a stable cell line expressing cloned human NK1R, the cDNA was subcloned into the vector pRcCMV (INVITROGEN). Transfection of 20 ug of the plasmid DNA into CHO cells was achieved by electroporation in 800 µl of transfection buffer supplemented with 0.625 mg/ml Herring sperm DNA at 300 V and 950 µF using the IBI GENEZAPPER (IBI). The transfected cells were incubated in CHO media [10% fetal calf serum, 100 U/ml penicillin-streptomycin, 2 mM glutamine, 1/500 hypoxanthine-thymidine (ATCC), 90% IMDM media (JRH BIOSCIENCES, Lenexa, KS, USA), 0.7 mg/ml G418 (GIBCO)] in 5% CO₂ at 37°C until colonies were visible. Each colony was separated and propagated. The cell clone with the highest number of human NK1R was selected for subsequent applications such as drug screening.

C. Assay Protocol using COS or CHO

The binding assay of human NK1R expressed in either COS or CHO cells is based on the use of ¹²⁵I-substance P (¹²⁵I-SP, from DU PONT, Boston, MA) as a radioactively labeled ligand which competes with unlabeled substance P or any other ligand for binding to the human NK1R. Monolayer cell cultures of COS or CHO were dissociated by the non-enzymatic solution (SPECIALTY MEDIA, Lavellette, NJ) and resuspended in appropriate volume of the binding buffer (50 mM Tris pH 7.5, 5 mM MnCl₂, 150 mM NaCl, 0.04

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mg/ml bacitracin, 0.004 mg/ml leupeptin, 0.2 mg/ml BSA, 0.01 mM phosphoramidon) such that 200 μ l of the cell suspension would give rise to about 10,000 cpm of specific ^{125}I -SP binding (approximately 50,000 to 200,000 cells). In the binding assay, 200 μ l of cells were added to a tube containing 20 μ l of 1.5 to 2.5 nM of ^{125}I -SP and 20 μ l of unlabeled substance P or any other test compound. The tubes were incubated at 4°C or at room temperature for 1 hour with gentle shaking. The bound radioactivity was separated from unbound radioactivity by GF/C filter (BRANDEL, Gaithersburg, MD) which was pre-wetted with 0.1% polyethylenimine. The filter was washed with 3 ml of wash buffer (50 mM Tris pH 7.5, 5 mM MnCl_2 , 150 mM NaCl) three times and its radioactivity was determined by gamma counter.

The activation of phospholipase C by NK1R may also be measured in CHO cells expressing the human NK1R by determining the accumulation of inositol monophosphate which is a degradation product of IP_3 . CHO cells are seeded in 12-well plate at 250,000 cells per well. After incubating in CHO media for 4 days, cells are loaded with 5 μCi of ^3H -myoinositol in 1 ml of media per well by overnight incubation. The extracellular radioactivity is removed by washing with phosphate buffered saline. LiCl is added to the well at final concentration of 10 mM with or without the test compound, and incubation is continued at 37°C for 15 min. Substance P is added to the well at final concentration of 0.3 nM to activate the human NK1R. After 30 min of incubation at 37°C, the medium is removed and 0.1 N HCl is added. Each well is sonicated at 4°C and extracted with CHCl_3 /methanol (1:1). The aqueous phase is applied to a 1 ml Dowex AG 1X8 ion exchange column. The column is washed with 0.1 N formic acid followed by 0.025 M ammonium formate-0.1 N formic acid.

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The inositol monophosphate is eluted with 0.2 M ammonium formate-0.1 N formic acid and quantitated by beta counter.

The data in Table 1 were obtained for compounds of formula (I):

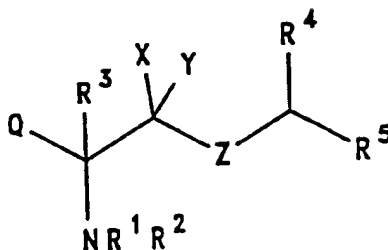
TABLE 1
SUBSTANCE P ANTAGONISM RESULTS

	<u>Compound of Ex #</u>	<u>IC₅₀ @ NK1R (nM)</u>
10	1	80
	2	70
	3	100, 190
	4	150
15	5	320
	6	250
	7	42% @ 1 μ M
	8	60
	9	300
20	10	300

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CLAIMS:

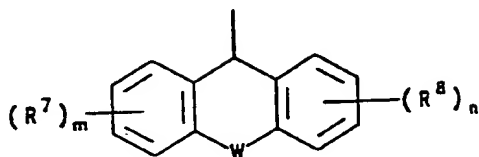
1. A compound of formula (I), or a salt or prodrug thereof:



(I)

wherein

15 Q represents a group



where W represents a bond, O, S, -CH₂CH₂-, -CH=CH- or a group NR⁶, where R⁶ is H or C₁₋₆alkyl and one or both of the phenyl rings may be replaced by a heteroaryl moiety;

25 X and Y each represent H or X and Y together form a group =O;

Z represents O, S or NR⁸, where R⁸ represents H or C₁₋₆alkyl;

30 R¹ and R² independently represent H; C₁₋₆ alkyl optionally substituted by hydroxy, cyano, COR^a, COOR^a, CONR^aR^b, COC₁₋₄alkylNR^aR^b, CONR^aC₁₋₄alkylCONR^aR^b or NR^aR^b, (where R^a and R^b each independently represent H, C₁₋₆ alkyl, phenyl (optionally substituted by one or more of C₁₋₆alkyl, C₁₋₆alkoxy, halo and trifluoromethyl) or

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phenyl(C₁₋₄alkyl) (optionally substituted in the phenyl ring by one or more of C₁₋₆ alkyl, C₁₋₆ alkoxy, halo and trifluoromethyl)); phenyl(C₁₋₄ alkyl), (optionally substituted by one or more of C₁₋₆ alkyl, C₁₋₆ alkoxy, halo and trifluoromethyl in the phenyl ring); C₂₋₆ alkylene; COC₁₋₆alkylhalo; COR^a; COOR^a; CONHR^a; COC₁₋₄alkylNR^aR^b; or CONR^aC₁₋₄alkylCONR^aR^b; (where R^a and R^b are as previously defined) or R¹ and R² together form a chain (CH₂)_p where p is 4 or 5 and where one non-terminal methylene group may optionally be replaced by an oxygen atom or a group NR^x, where R^x is H or C₁₋₆ alkyl;

R³ represents H or C₁₋₆alkyl;

R⁴ represents H, C₁₋₆ alkyl or phenyl (optionally substituted by one or more of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^c, SOR^c, SO₂R^c, OR^c, NR^cR^d, NR^cCOR^d, NR^cCOOR^d, COOR^c or CONR^cR^d, where R^c and R^d each independently represent H, C₁₋₆ alkyl, phenyl or trifluoromethyl);

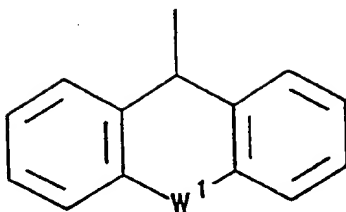
R⁵ represents (CH₂)_qphenyl, wherein q is 0, 1, 2 or 3 which may optionally be substituted in the phenyl ring by one or more of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^c, SOR^c, SO₂R^c, OR^c, NR^cR^d, NR^cCOR^d, NR^cCOOR^d, COOR^c or CONR^cR^d, where R^c and R^d are as above defined;

each R⁷ and R⁸ independently represents C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halo, cyano, nitro, trifluoromethyl, trimethylsilyl, SR^c, SOR^c, SO₂R^c, OR^c, NR^cR^d, NR^cCOR^d, NR^cCOOR^d, COOR^c or CONR^cR^d, where R^c and R^d are as above defined; and

m and n independently represent 0, 1, 2, 3 or 4.

2. A compound as claimed in claim 1 wherein Q represents a group

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where W^1 is a bond, O, S or a group NR^6 , where R^6 is H or C₁₋₆ alkyl;

R^1 and R^2 each independently represent H, C₁₋₆ alkyl, phenyl(C₁₋₄ alkyl), COR^{10} , $COOR^{10}$ or $CONHR^{10}$,
 10 where R^{10} is C₁₋₆ alkyl or phenyl;

R^4 represents H, C₁₋₆ alkyl or phenyl (optionally substituted by one or more of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halo, cyano, nitro, trifluoromethyl, SCH_3 ,
 15 $SOCH_3$, SO_2CH_3 , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ or $CONR^C R^d$ (where R^C and R^d are as above defined); and

R^5 represents $(CH_2)_q$ phenyl, wherein q is 0, 1, 2 or 3 which may optionally be substituted by one or more of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halo, cyano,
 20 nitro, trifluoromethyl, SCH_3 , $SOCH_3$, SO_2CH_3 , OR^C , $NR^C R^d$, $NR^C COR^d$, $NR^C COOR^d$, $COOR^C$ or $CONR^C R^d$ (where R^C and R^d are as above defined);

wherein any phenyl (including benzyl) ring in the definitions of R^1 or R^2 (including R^{10}) above may be
 25 optionally substituted by one or more of C₁₋₆ alkyl, C₁₋₆ alkoxy, halo or trifluoromethyl.

3. A compound as claimed in claim 1 or claim 2 wherein W represents a bond.

30

4. A compound as claimed in claim 1 wherein W represents CH_2CH_2 or $HC=CH$.

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5. A compound as claimed in any one of claims 1 to 4 wherein X and Y each represent H and Z represents O.

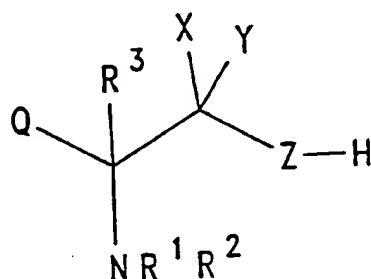
6. A compound as claimed in any one of claims 1 to 5 wherein R⁴ is H and R⁵ is substituted phenyl.

7. A compound as claimed in claim 1 selected from:
1-(5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine;
10 N-acetamido-1-(5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine;
1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine;
N-acetamido-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine;
15 N,N-dimethyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-dimethylbenzyloxy)ethylamine;
1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-bistrifluoromethylbenzyloxy)ethylamine;
20 N-carbomethoxymethyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-bistrifluoromethylbenzyloxy)ethylamine;
N-carbamoylmethyl-1-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-2-(3,5-bistrifluoromethylbenzyloxy)ethylamine;
25 3,5-dimethylbenzyl-2-(9-fluorenyl)glycinate;
3,5-dimethylbenzyl N-acetyl-2-(9-fluorenyl)glycinate;
and salts and prodrugs thereof.

8. A compound as claimed in any one of the preceding claims for use in therapy.

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9. A process for the preparation of a compound as claimed in any one of claims 1 to 7 which process comprises reaction of a compound of formula (II):



(II)

15 wherein Q, R¹, R², R³, X and Y are as defined for formula (I) and Z is O or S, with a compound of formula HalCHR⁴R⁵ where R⁴ and R⁵ are as defined for formula (I) and Hal is halo, in the presence of a base, and, if necessary or desired, converting the compound of formula (I) so
20 prepared to another compound of formula (I), or a salt or prodrug thereof.

10. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 7 in association with a pharmaceutically acceptable carrier or
25 excipient.

11. A method for the treatment or prevention of a physiological disorder associated with an excess of tachykinins, which method comprises administration to a
30 patient in need thereof of a tachykinin-reducing amount of a compound according to claim 1.

12. A method according to claim 11 for the treatment or prevention of pain or inflammation.

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13. A method according to claim 11 for the treatment or prevention of migraine.

5 14. A method according to claim 11 for the treatment or prevention of postherpetic neuralgia.

INTERNATIONAL SEARCH REPORT

PCT/GB 92/01212

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5	C07C217/48; C07C233/31;	C07C233/22; C07D311/90;
	C07C229/14; C07D335/20;	C07C237/20 C07D219/02
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07C ; C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	DE,A,2 035 535 (CENTRE EUROPEEN DE RECHERCHES MAUVERNAY) 28 January 1971 see page 15, line 4 - page 19, line 21; claims 1,9; examples 18,19	1,8, 10-14
A	CHEMICAL ABSTRACTS, vol. 64, 1966, Columbus, Ohio, US; abstract no. 8294b, see abstract & ZH. ORGAN. KHIM. vol. 1, no. 11, 1965, pages 2069 - 2071 V.I. RYABOI ET AL & REGISTRY (Database, STN) RN: 5364-42-1	1
-/--		
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
25 NOVEMBER 1992	15 DEC 1992	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	VAN AMSTERDAM L.	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category ^a	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	GB,A,2 054 588 (SOCIETE INDUSTRIELLE DE PRODUITS DE SYNTHESE) 18 February 1981 see page 8, line 20 - page 9, line 27; claims ---	1,8, 10-14
A	EP,A,0 394 989 (FUJISAWA PHARMACEUTICAL CO LTD) 31 October 1990 cited in the application -----	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB92/01212

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 11-14 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9201212
SA 62450**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 25/11/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-A-2035535	28-01-71	FR-A- 2054507	23-04-71
GB-A-2054588	18-02-81	FR-A- 2460919	30-01-81
		BE-A- 884212	08-01-81
		CA-A- 1148547	21-06-83
		CH-A- 644348	31-07-84
		DE-A, C 3026201	26-02-81
		JP-C- 1447121	30-06-88
		JP-A- 56015250	14-02-81
		JP-B- 62053504	10-11-87
		NL-A- 8003601	13-01-81
		US-A, B 4301163	17-11-81
EP-A-0394989	31-10-90	JP-A- 3027399	05-02-91